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EDITORIAL

A Never Ending Story in the Pursuit of Susceptible Genes in Allergy and Asthma

Jiu-Yao Wang*

Department of Pediatrics, College of Medicine, National Cheng Kung University, Tainan, Taiwan

The prevalence of complex genetic immune disorders, such as asthma, has escalated in recent decades. Although tremendous effort has been expended to localize the susceptibility genes in complex genetic disorders such as asthma, elucidation of the multigenic nature of asthma has been greatly hampered by genetic heterogeneity across populations, variability in disease expression, phenocopies and uncontrolled environmental influences.[1] Moreover, there may be various forms of asthma that involve different components of genes and environmental interactions.[2] Today, over 100 variants in candidate genes have been reported to be associated with the phenotypes of allergic asthma. The main regions of these variants are on chromosomes 2q, 5q, 6p, 11q, 12q, 16 q and 17 q.[3] Several *de novo* genes or previously unidentified genes related to allergy or asthma have been identified using a positional approach.[3] In Taiwan, there have been several important studies on the genetic components of allergy and asthma in our population.[4–17]

In this issue of the journal, Huang et al[18] reported that a LT-α-NcoI polymorphism in the lymphotoxin-α (LT-α) gene, located on chromosome 6p21.1, was associated with atopic asthma in the sample population of 114 asthmatic children and 155 non-asthmatic controls. Although the difference between wild type and variant type of this genetic polymorphism was significant (p=0.031), the findings of this small-scale study in a very complex disease such as allergic asthma raise several issues for further investigation. The first issue is regarding the methodology. Given the complexity of asthma, it may be inappropriate to conduct the study using methodologies and statistics originally devised for the study of simple (single gene) genetic disorders. It is therefore unsurprising that even well-conducted research throws up apparently contradictory results, such as the conflicting results of LT-α-NcoI polymorphism in different populations of Japan,[19,20] or in the same ethnic background reported from Kaohsiung in Taiwan.[21] The second issue is regarding how clear-cut phenotypes can be defined that fit the complex nature of allergy and asthma. Allergy does not equal asthma. Even the definition of allergy needs to be very strictly denoted as the elevation of allergen specific-positive IgE present or the history of allergic symptoms. In the real world, these two are not equal. Moreover, asthma phenotype is variable within populations. It is also variable within the same individual. Over a period of months or years, the expression of the disease may change dramatically.[22] Previously, we conducted a genome-wide linkage disequilibrium screen for loci associated with genetic differences between allergic and non-allergic asthma using 763 autosomal short tandem repeat markers in 200 unrelated asthmatic children. We found that there was a significant difference in genetic profiles between allergic and non-allergic asthmatic children.[10] Therefore, studies should, if possible, address the variable nature of the disease with a clear phenotype definition. Finally, it is well recognized that a significant

*Corresponding author. Department of Pediatrics, College of Medicine, National Cheng Kung University, 138 Sheng-Li Road, Tainan 704, Taiwan.
E-mail: a122@mail.ncku.edu.tw

flaw in much existing work is the relatively low power of individual studies. This has resulted in relatively high false-positive probabilities for reported associations. Future studies are likely to involve increasing collaboration between different centers, as increasing the size (and hence power) of any study, or prospectively following up subjects from birth to 6 years of age as Taiwan birth cohorts, may help to reduce these errors and provide valuable information with regard to the "genesis" of allergy and asthma.

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